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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/637,190	08/11/2000	Mien-chie Hung	12005-002001	8780

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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	17

DATE MAILED: 07/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/637,190	Hung et al
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-20* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ *are subject to restriction and/or election requirement.*

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ *Notice of References Cited* (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ *Interview Summary* (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 1-20 are pending and under consideration.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

3.The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, 4, 6, 7, 9, 11, 12, 14, 16, 17 and 19 are vague and indefinite in the recitation of "threshold level". The term "threshold level" in claims 1, 6, 11 and 16 is a relative term which renders the claims indefinite. The term "threshold level" is not defined by the claims, the specification does not provide a definition of "threshold level" wherein one of ordinary skill in the art would be reasonably apprised of the scope of the invention. The specification describes methods by which the "threshold level" can be empirically determined on page 2, lines 3-10. However, this does not constitute a limitation whereby the metes and bounds of the claims can be determined. Furthermore, It is noted that the specification states "The threshold levels of expression for exclusion or inclusion in any group is set to achieve pre-determined levels of survival". Thus, a pre-determined survival probability must be known in order to segregate patients on the basis of Maspin expression. As the claims 1-10 are drawn to determining a probability of survival, it appears that the guidance given in the specification is not adequate for the determination of a "threshold level".

5. Claims 1-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sager et al (USP 5,470,970) in view of the abstracts of Ding et al (Proc Amer Assoc Cancer Res, 1996, Vol. 37, page 90) , and Rheinwald et al (Cancer Research, 1981, Vol. 41, pp. 1657-1663) and Pemberton et al (J. Of Histochemistry & Cytochemistry, 1997, Vol. 45, pp. 1697-1706) and the abstracts of Petrovich et al (Radiology, 1982, Vol. 144, pp. 905-908) and Weber et al (Otolaryngology-Head and Neck Surgery, 1988, Vol. 99, pp. 16-23) and Tytor et al (Clinical Otolaryngology, 1990, Vol. 15, pp. 235-252) and Eiband et al (American Journal of Surgery, 1989, Vol. 158, pp. 314-317) and Huwer et al (European Journal of Cardio-Thoracic Surgery, 1992, Vol. 6, pp. 498-502) and Nagel et al (Zentralblatt fur Chirurgie, 1994, Vol. 119, pp. 225-232) and van der Velden et al (Cancer, 1995, Vol. 75, pp. 2885-2890).

Claim 1 is drawn to a method of determining the probability of survival for a subject with squamous cell carcinoma, the method comprising determining the level of Maspin gene expression in a biological sample and comparing said level with a threshold level, wherein a level of gene expression in the biological sample which is above the threshold level is indicative of a relatively high probability of survival. Claim 6 is drawn to a method of determining the probability of survival for a subject with squamous cell carcinoma, the method comprising determining the level of Maspin gene expression in a biological sample and comparing said level with a threshold level, wherein a level of gene expression in the biological sample which is below the threshold level is indicative of a relatively low probability of survival. Claim 11 is drawn to a method of determining whether a subject with squamous cell carcinoma does not have a lymph node containing cancerous cells, the method comprising determining a level of Maspin gene expression in a biological sample and comparing the level with a threshold level, wherein a level of Maspin gene expression above the threshold level is indicative that the subject does not have a lymph node containing cancerous cells. Claim 16 is drawn to a method of determining whether a subject with squamous cell carcinoma does not have a lymph node containing cancerous cells, the method comprising determining a level of Maspin gene expression in a

biological sample and comparing the level with a threshold level, wherein a level of Maspin gene expression below the threshold level is indicative that the subject has a lymph node containing cancerous cells. Claims 2, 7, 12 and 17 embody the methods of claims 1, 6, 11 and 16 respectively, wherein Maspin gene expression is determined by measuring Maspin protein. Claims 3, 8, 13 and 18 embody the methods of claims 2, 7, 12 and 17 respectively, wherein the amount of Maspin protein is determined by an antibody that specifically binds to Maspin. Claims 4, 9, 14 and 19 embody the methods of claims 1, 6, 11 and 16, respectively, wherein Maspin gene expression is determined by measuring Maspin mRNA. Claims 5, 10, 15 and 20 embody the methods of claims 4, 9, 14 and 19, respectively, wherein the level of Maspin mRNA is determined by Northern Blot.

Sager et al teach a method for staging a carcinoma wherein the carcinoma is derived from cells which normally express the Maspin gene, said method comprising the detection of Maspin gene mRNA by northern blot. Sager et al teach that wherein the amount of hybridization complex detected is less than about one-half, more preferably less than about one-third, and more preferably less than about one-tenth the amount found in the non-cancerous control cell, the quantity of said hybridization complex is indicative that the test cell is cancerous, whereas the absence of a hybridization complex with the mRNA of the test cell is indicative that the test cell is from an advanced, probably metastatic carcinoma. Sager et al teach determination of the hybridization complex by Northern Blot (column 4, lines 24-57). Sager et al also teach the detection of the Maspin protein by means of monoclonal or polyclonal antibodies, and the same correlation between the relative level of the immunocomplex in the test sample to the control sample (column 4, line 58 to column 5, line 15). Thus, Sager et al teaches the correlation between Maspin gene expression in carcinomas and the relative likelihood of metastasis. Sager et al does not specifically teach squamous cell carcinoma as a type of carcinoma, but teaches that the suspected carcinoma is derived from a type of cell which normal expresses the Maspin gene to a significant and easily detectable degree (column 4, lines 21-26).

The abstract of Ding et al teaches that the squamous cell carcinoma line of SCC4 highly expresses the Maspin protein. The abstract further teaches that Maspin plays a role in several human tumors including those of the tongue and endometrium and that Maspin was commonly overexpressed in squamous cell carcinomas.

Rheinwald et al teach that the SSC4 cell line was derived from human squamous cell carcinoma of the tongue (page 1658, first column, lines 2-3).

Pemberton et al teach that Maspin is highly expressed in the endometrium of the uterus and the squamous epithelium of the tonsil (page 1701, second column, lines 6-15 under the heading "Discussion").

The abstract of Petrovich et al and Weber et al and Tytor et al and Eiband et al and Huwer et al and Nagel et al and van der Velden et al all teach the correlation between metastasis to lymph nodes and poor survival in patients having squamous cell carcinoma.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to correlate the absence of a hybridization complex or an immunocomplex with metastasis to the lymph nodes and poor probability of survival in patients having squamous cell carcinomas of the tongue, uterine endometrium or tonsil; it would also have been obvious to correlate the decrease of Maspin gene expression with an early stage carcinoma that is probably not metastatic with relatively high probability of survival and a low probability of lymph node metastases in patients having squamous cell carcinomas of the tongue, uterine endometrium or tonsil. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Sager et al on the correlation between Maspin gene expression and the likelihood of metastasis in carcinomas derived from a cell type which normally expresses Maspin, the teachings of the abstract of Ding et al on the common over expression of Maspin in squamous cell carcinomas and the role of Maspin expression in human tumors of the tongue and endometrium, the teachings of Pemberton et al on the expression of Maspin in normal tissues of the uterine endometrium and the tonsil. One of

skill in the art would have recognized that squamous cell carcinomas of the tongue, uterine endometrium and tonsil are carcinomas derived from a type of cell which normally expresses the Maspin gene, and thus the correlations of Maspin expression and metastatic cancer as taught by Sager et al apply to squamous cell carcinomas of the tongue, uterine endometrium and tonsil. Further one of skill in the art would recognize that the presence of lymph node metastases would be prognostic for poor survival in patients with squamous cell carcinoma according to the teachings of Petrovich et al and Weber et al and Tytor et al and Eiband et al and Huwer et al and Nagel et al and van der Velden et al.

6. All other rejections and objections as set forth in Paper No. 13 are withdrawn.

Conclusion

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
June 30, 2003